March 20, 1950.

Mr. Gordon Allen,
155 Corona Avenue,
Pelham 65, N.Y.

Dear Gordon:

Thanks for the very interesting details on your experimental progress. I had not bothered to mention it, but Mal is, of course, not the only factor with a peculiar behavior. Xyl, Mtl, and even Gal and Ara also show linkage anomalies, and peculiar segregation behavior from persistent diploids that would have led me to predict that they would not give complementary ratios in your nutritionally complementary recombinants. Your technique is an important and powerful one which should be thoroughly exploited.

It is a strange coincidence that the first several factors that I studied for linkagesshould have seemed to show more straightforward behavior than all of these others. I have no data to suggest that the linear order of M V6 Lac TL should be questioned. I would like to urge you, in the strongest terms, to study V6, Lac and V1, in particular, for normal reciprocal ratios among complementary recombinants, because if any sense is ever to be made out of segregation in E. coli K-12, this background of linear linkage and mendelization for at least some factors must be very thoroughly investigated. If, as you suggest, and some of my Yale data confirm, Az is located towards TL, it might also be useful.

Cytologically, the notion of two "chromosomes" might fit better than just one. There is now no very good reason to regard the Mal-Xyl-Mtl-... complex as linked to M, and some rather difficult to interpret data from diploids also suggests their independence. On the other hand, the peculiarities of this second complex are such as to make it dangerous to assign it to any chromosome.

I am not sure that I go along with you in regarding the segregation peculiarities as "non-meiotic", except in the loosest sense. The fact that diploids are often already peculiar (hemi- or homozygous) suggests that the aberrations are not the immediate result of a mysterious segregation process from a normal heterozygous diploid, but rather that the zygote itself does not have, or does not always retain the constitution expected of it. I would prefer to think that a normal synkaryon is formed at fertilization, and that there are subsequent irregularities, including elimination and autogamic homozygotization, but it is also conceivable that fertilization itself might be imperfect. There are,however, somewhat involved reasons why this might hot be so.

I have no brief for the retention of the biotin requirement in 58-161. At Yale, I did recover B- recombinants, but the stock might certainly have altered since then. Do you have 58- so that you are familiar with the responses of this mutant? One of Lardy's students found almost complete replacement with certain amino acids.

If you have any ingenious time-saving methods, by all means let me know.

Some time ago, Zinder also went to some trouble to prepare, not quadruple, but at least double mutants, from K-12. The more the merrier, but I hope you are acquainted with W: 758, 760, 761, 826, 828, 831, 832, all of which are double amino-acid mutants, from K-12. Also, W-848 [which was not sent with the batch to Bernie about a year ago] is a Lac- from W-826, and 853 a Lac- from 828. If any of these could be any help to you, say the word. You should have no trouble at all getting fermentative mutants from any of your cultures. You may have some difficulty in hitting the same loci, as those you are now studying in W-677, as you can only tell this by allelism tests after the mutants are isolated. One tip you might not have been aware of: check any mutants on all sugars, especially glucose, galactose and maltose, to avoid pleiotropic effects, which are not uncommon. The pleiotropic mutants are rather troublesome as genetic markers, and are probably best discarded before bothering much with them.

From the rather limited work I've done with new sets of mutants, I would conclude that the meiotic troubles are not confined to 58- and 679- descendants.

I hadn't thought it through that you would get such a high proportion of B_1-P- from BMP x TLB_1. Some data at Yale gave me the impression that a P- I had there was almost exactly equidistant from Lac and Vl, between them; if 90% of the quasi-prototrophs on Bl-P agar are Bl-P-, then P must be rather further towards TL, or have I not understood you properly.

I rather hesitate, just yet, at the conclusion that you have complementaries from the same zygote— you point out yourself the necessary criteria. Owing to syntrophic growth, the density of recombinants surrounding a quasi-prototroph might be at least a little higher than on the plate as a whole; alternatively, the complementaries might not occur at the same rate [Do you have some direct data?]. Are your platings for P/ principals done with very dilute suspensions, to give very few recombinants per plate?

Sincerely,

Joshua Lederberg

P.S. As I've tried to convince you before, and will continue, you are obviously too good at this sort of work to leave it conscientiously. Won't you reconsider?